Central Aortic Blood Pressure and Management of Hypertension

Confirmation of a Paradigm Shift?

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See related article, pp 1138–1145

Hypertension, a condition of elevated arterial blood pressure (BP) conventionally diagnosed by brachial cuff sphygmomanometry, is associated with increased risk of cardiovascular mortality and morbidity and end-organ damage. However, the marked differences in pulse pressure between the central aorta and peripheral limbs1 suggest that effects of peak values of arterial BP (eg, systolic BP) on centrally located organs (heart, brain, kidney) may not be accurately assessed using peripheral measurements. Our early studies2 showed substantial difference in the effects of sublingual nitroglycerin on peripheral and central systolic BP. There were, however, marked changes in the pulse wave form.2

The relationship between central aortic and radial pressure waves, quantified in terms of a mathematical transfer function, has been validated to be applicable across a large range of physiological pressures.3 The use of this noninvasive technique (and other variations, including other forms of analysis of the radial pulse or direct registration of the carotid pulse) has facilitated a large number of studies highlighting the differential effects of antihypertensive therapy on central aortic systolic BP for similar values of brachial cuff systolic BP.4 A seminal study by McEniery et al5 in >10000 subjects demonstrated a substantial overlap of central and brachial BP between categories of hypertension. Approximately 32% of men and 10% of women who would be considered to have normal brachial systolic BP (and therefore, not treated) would be classified as having stage 1 hypertension based on equivalent central aortic systolic BP. Indeed, the implications of these findings suggested a possible sign of a paradigm shift in the management and treatment of hypertension as a significant cardiovascular risk.6 Subsequent studies produced additional evidence of the possibility of added value of central aortic BP. In the assessment of modern combination therapies, the amlo- dipine–valsartan combination was shown to decrease central aortic systolic BP to a greater extent than the amlodipine–atenolol combination for a similar effect on brachial systolic BP.7 Central pulse pressure has also been shown to be superior to ambulatory BP in the prediction of all-cause and cardiovascular mortality.8 However, notwithstanding these and other studies, there is still insufficient evidence for central aortic BP to be integrated in guidelines for treatment and management of hypertension.9

The study by Sharman et al10 in this issue of Hypertension addresses the use of central aortic BP as an additional measure in the management of hypertension. However, in contrast to other studies that perform a comparison of effects of treatments2,4,7 or risk categories,5,8 this study uses central aortic BP as a guide for treatment. Although conducted in a relatively small population (286 hypertensive patients), the study is particular in both the design and the relevance of the demonstration of the added value of central aortic BP. It is a prospective, randomized, open-label, blinded end point (PROBE) study in which patients were randomized to treatment decisions that were guided by best-practice usual care for BP (n=142; using office BP, home BP, and 24-hour ambulatory BP) or the addition of a central aortic BP intervention (n=144) where central aortic BP was measured using radial applanation tonometry (SphygmoCor). The study duration was 12 months, and therapy was reviewed at intervals of 3 months.

A key element of the study is the guidelines and recommendations given to the treating practitioners for titration of therapy. The 5 recommendation scenarios describe the combination of central aortic BP with the other BP measures (office, home, 24-hour ambulatory BP) so as to increase, maintain, or decrease the therapy. In addition to reaching the target BP using the conventional brachial cuff values, the study contains 3 specific outcome measures: the World Health Organization standard metric for quantity of medication (daily defined dose [DDD]), quality of life questionnaire, and left ventricular (LV) mass obtained by 3-dimensional echocardiography.

The study shows an impressively high adherence (92%) by practitioners and patients to the recommendations, with an improvement of quality of life in both groups. The usual care BP group showed no change in DDD, whereas the central aortic BP group showed a progressive decrease in DDD at each of the 3-month intervals for a similar level of brachial cuff BP between the groups. The study demonstrates for the first time that if central aortic BP is included in the measurement and is also used as a guide to titrate therapy, a similar target brachial BP can be achieved with a reduction in medication as quantified by DDD. In addition, there was a much higher proportion

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of subjects in the central aortic BP group that ceased medication altogether (16%) compared with the usual care group (2%). All groups showed no statistical difference in LV mass, but the central aortic BP group showed a trend for a reduction, whereas the usual care group showed a trend for an increase. Although the effects were relatively small (change in LV mass of \(0.26\) g), the statistical significance is borderline \((P=0.079)\). There was also no difference in aortic pulse wave velocity in all the groups, although this is not surprising, given that the values of mean and diastolic pressures were similar in both groups.

Although demonstrating a potential for added value of central aortic BP in guiding hypertension management, the study by Sharman et al\(^\text{10}\) raises several questions on the underlying significance of the results and the conclusions reached. One issue is the effect of heart rate on the relationship between central and radial pulse pressure\(^1,3\) as was seen in the studies assessing the effects of \(\beta\)-adrenergic blockade (atenolol) as a hypertensive treatment\(^4\), where central aortic systolic pressure was shown to be relatively higher than the amlodipine group for similar brachial systolic pressure. However, this was not a significant concern in the study by Sharman et al\(^10\) because only \(\approx 7\%\) of subjects in the whole cohort were on \(\beta\)-blockers, and there was no difference in heart rate among the groups.

The other issue is the effects of age on the normal BP values. For both brachial and central aortic BP, the range of normal values used in the study increased with age. The authors make the valid point that, indeed, a decrease in DDD could also be achieved simply because of the fact that the target BP values would increase with age, hence requiring reduced medication. However, a plausible explanation for this is offered, which is supported by the findings of the effects of central aortic BP-guided therapy on LV mass index. If the marked reduction of DDD in the central aortic BP group occurred because of a fortuitous coincidence of the effects of age caused by increased target values, there would be an expected rise in LV mass index, presumably because of an attenuated effect of treatment on BP. However, the study found the opposite: a reduced DDD in the central aortic BP group was associated with a trend for reduced LV mass index.

From the results of this study, the authors make the potentially powerful assertion that antihypertensive therapy guided by central aortic BP provides a more appropriate form of treatment. Thus, the suggestion is that this may provide the groundwork for the introduction of central aortic BP in the clinical management of hypertension. However, an apparent limitation of the study is that the use of central aortic BP would seem to be more effective in those with a large difference between central aortic and brachial systolic pressure. This is predominantly seen in younger individuals because the largest difference in central and peripheral systolic pressure is seen in age groups below the fifth decade of age, whereas the majority of hypertensive individuals are \(>50\) years of age. However, a difference of \(\approx 11\) mm Hg has been found to persist till the age of \(80\)\(^4\), which was similar to the mean difference found in the study by Sharman et al\(^10\) for a mean age of \(64\) years. This indicates that the procedure could still be of benefit in the elderly, although future studies would need to produce data on threshold differences where central aortic BP would not improve treatment.

The 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the management of arterial hypertension\(^7\) state that although the measurement of central aortic BP is of interest in terms of analyses for elucidating mechanisms related to pathophysiology, pharmacology, and therapeutics, further investigations are needed before central aortic BP can be recommended for routine clinical use (with the only possible exception being isolated systolic hypertension in youth). Indeed, trials are required to assess hard end points, where subjects are followed up for a longer period (of the order of \(5\) years, similar to many other intervention studies). In addition, the design should be expanded where central aortic BP is measured in all subjects, but where one group is assessed by measurements of brachial cuff pressure but blind to the results of central BP and the other groups guided by the results of central BP but blind to the results of brachial BP. The study by Sharman et al\(^10\) provides the basis for these further investigations. It provides clear evidence that the addition of central aortic BP can improve management of hypertension. However, although the intention of the PROBE design is to provide results that would be applicable to the real-world methods used by practitioners to treat and manage hypertension, it is not known to what extent this design contributed to any underlying bias among practitioners who were using the additional and novel measurement of central aortic BP. In this and other studies, central aortic BP was estimated using applation tonometry. The requirements for operator training and additional time required for the procedure limit the practical use in the clinical setting, and to date central aortic BP has been essentially an informative research tool. However, with new devices that are able to measure central aortic BP using the conventional brachial cuff, future studies will have the capacity to be expanded to include both office and 24-hour central aortic BP measurements.

The overlap between brachial and central BP found in the study of McEniery et al\(^5\) among categories of hypertension implies that based simply on the brachial cuff BP, but in reference to the effects of central aortic BP on end-organ damage, there are some individuals who should be treated and who are not and others who are on treatment and perhaps might not require it. The paradigm shift that was suggested by these observations\(^6\) would now seem to be supported by novel (although limited) confirmatory evidence from the study of Sharman et al\(^10\), where the use of central aortic BP to guide therapy is shown to provide improvement in the efficacy of management of hypertension through reduction of medication, as well as an additional effect with the possibility of reducing LV mass for similar values of brachial cuff systolic BP. The logical consequence of the confirmation of this paradigm shift is a potential pathway for the consideration of inclusion of central aortic BP in the clinical management of hypertension.

Disclosures

None.

References


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